PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference MNL6	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB2004/000198	International filing date *(day/month/year)* 21.01.2004	Priority date *(day/month/year)* 23.01.2003
International Patent Classification (IPC) or both national classification and IPC C07D487/04		
Applicant MOLECULARNATURE LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.08.2004	11.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fritz, M Telephone No. +49 89 2399-2792

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB2004/000198

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-55 as originally filed

Claims, Numbers

1-44 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☒ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21-33

   because:

   ☒ the said international application, or the said claims Nos. 21-33 with respect to industrial applicablity relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20,34-44
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20,34-44
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-20,34-44
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 21-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

It is noted that an International Preliminary Examinationis carried out only on the subject-matter actually searched (cf. Interational Search Report, Sheet C; Rule 66.1 e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: BELL A A ET AL: "Synthesis of Casuarines [Pentahydroxylated Pyrrolizidines] by Sodium Hydrogen Telluride-Induced Cyclisations of Azidodimesylates" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 33, 18 August 1997 (1997-08-18), pages 5869-5872, XP004085896 ISSN: 0040-4039

D2: WORMALD M R ET AL: "Configurational and conformational analysis of highly oxygenated pyrrolizidines: definitive identification of some naturally occurring 7a-epi-alexines" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 9, no. 14, 17 July 1998 (1998-07-17), pages 2549-2558, XP004131419 ISSN: 0957-4166

D3: NASH ET AL.: "Casuarine: A very Highly Oxygenated Pyrrolizidine Alkaloid" TETRAHEDRON LETTERS, vol. 35, no. 42, 1994, pages 7849-7852, XP002274756

D4: DENMARK ET AL.: "Synthesis of (+)-Casuarine" ORGANIC LETTERS, vol. 1, no. 8, 1999, pages 1311-1314, XP002274757

D5: DENMARK ET AL.: "Synthesis of (+)-Casuarine" J. ORG. CHEM., vol. 62, 2000, pages 2875-2886, XP002274758

D6: WORMALD M R ET AL.: "Casuarine-6-alpha-D-Glucoside from Casuarina Equisetifolia and Eugenia Jambolana" CARBOHYDRATE LETTERS, vol. 2, no. 3, 1996, pages 169-174, XP009028337 ISSN: 1073-5070

The present application relates to polyhydroxylated pyrrolizidine compounds for use in therapy (claims 1-20, 42-44), methods of treatment by administering these compounds (claims 21-33), the usage thereof for the preparation of a medicament (claims 34, 36), a process for the preparation of a medicament involving the use of these compounds (claim 35), pharmaceutical compositions thereof (claims 37-38), a vaccine thereof (claim 39) as well as a pharmaceutical kit thereof (claims 40-41).

For the assessment of the present claims 21-33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Casuarine, silylated derivatives thereof as well as casuarine-6α-D-glucoside are - as was also ackowledged in the description - known in the art (cf. D1-D6). Their pharmacological activities (inhibition of glycosidase) and use in the treatment of various diseases (cancers, AIDS and other viral diseases, diabetes, bacterial infections, diarrhoea, dysentery, colic) is also known.

It is - in this respect - noted that only the EPO considers a known compound for use in therapy novel, if a medical use of this compound has not been described so far.

Isolated casuarine itself as well as casuarine derivatives are known in the art, however a medical use of the isolated compounds has not been described yet. The only medical use described is that of plant extracts comprising - among other ingredients - casuarine and certain derivatives thereof.

Therefore the disclosures of D1-D6 are not detrimental for the novelty of claims 1-20 and 34-44 (Art. 33(2) PCT).

Acylated derivatives of casuarine are not known in the art, nor are compositions, vaccines or pharamceutical kits as referred to in claims 37-41 explicitly described.

The problem of the present application was to provide further compounds which may serve as immunomodulators.

This problem has been solved by casuarine and selected derivatives thereof, as can be seen in the description.

As casuarine and its derivatives are not known as having immunomodulating properties, they cannot be considered obvious for the skilled man, and an inventive step is acknowledged for the subject-matter of claims 1-20 and 34-44.

Further objections:

To fulfil the requirements of Article 6 PCT, the term "derivative thereof" employed in claims 1, 2, 16-22 should be substituted by "acylated derivative thereof" (cf. p. 20, 3rd paragraph).